

Comprehensive *In Vitro* ProArrhythmia Assay Schema

***Further Considerations
DRAFT (Is-Is not-Theme)***

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***For discussion of the Comprehensive
in Vitro ProArrhythmia Assay Group.***

Comprehensive *In Vitro* ProArrhythmia Assay (CiPA)

What It Is: Proposal to evaluate proarrhythmic risk based on mechanistic electrophysiologic understanding of proarrhythmia with two primary components

- I. *In vitro* drug effects, multiple cardiac channels
+
In silico reconstruction of electrical effects
- II. Confirmation using human stem-cell derived cardiomyocytes

What It is Not: Approach that negates well-controlled preclinical *in vivo* ECG assessment in preclinical studies

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What It Will Do:

- Prevent early (often unwarranted) attrition due to early testing for hERG liabilities with updated technologies and knowledge of proarrhythmia
- Provide a more complete assessment of proarrhythmic risk (rather than surrogate QT prolongation alone)
- Replace TQT study (high sensitivity) for higher specificity, less “false positives” based on functional hERG studies
- Potentially “rescue” drugs mislabeled with risk warnings by small degrees of QT prolongation in TQT studies

What It Will Not Do:

- Not replace need for careful clinical assessment of electrophysiologic effects in phase 1 ECG safety studies

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- What It Is:** Reflection of evolving practices by some Pharma for early *in vitro* detection of QT prolongation
- Regression techniques predict proarrhythmia from *in vitro* effects of 3 currents better than hERG assessment alone (Kramer et al, 2013)
 - In silico reconstructions show that hERG block may be mitigated by other (e.g. calcium) channel block (Mirams et al., 2011)
 - Recognition that hERG represents only one of multiple ion currents defining cardiac repolarization (surrogate marker of proarrhythmia)

What It Is Not: Novel approach never considered or employed by pharma, academics as part of exploratory/frontloading safety studies

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What It Is: Proposal to be developed by numerous stakeholders (Regulators, Pharma, Academics, CRO's)

- An evolving initiative with evolving workflows in need of wide participation and input of multiple parties
- A proposal that needs to be qualified

What It is Not: Predetermined or predefined regulatory schema with undue influence of vendors

- An approach that will render useless various approaches for internal decision-making (e.g., binding studies, *in-vivo* studies, other useful alternatives)

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What It Will Do:

- Standardize *in vitro* assays used to characterize drug effects, standardize *in silico* models, establish best practices for stem-cell derived cardiomyocyte models (comparable to “acceptable” TQT studies evolved)
- Provide proarrhythmic ranking based on calibration/validation efforts with agree-upon standards
- Likely lead to revision of S7B, E-14 guidelines, more sophisticated ECG modeling of drug effects in future

What It Will Not Do:

- Maintain regulatory status-quo for an imperfect surrogate marker of proarrhythmia
- Replace biological studies with fully integrated systems